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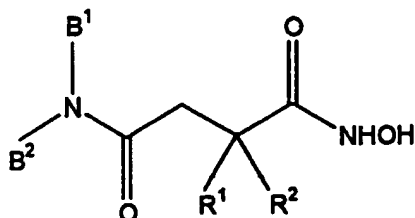
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(54) Title: HYDROXAMIC ACID DERIVATIVES AS MATRIX METALLOPROTEINASE (MMP) INHIBITORS



(I)

(57) Abstract: Compounds having therapeutic utility are of
formula (I) wherein B¹, B², R¹ and R² are each various sub-
stituents, or R¹ and R² together form a ring.

HYDROXAMIC ACID DERIVATIVES AS MATRIX METALLOPROTEINASE (MMP) INHIBITORS

Field of the Invention

This invention relates to hydroxamic acid derivatives, and to their use in medicine.

5 Background to the Invention

Metalloproteinases, including matrix metalloproteinase (MMP), (human fibroblast) collagenase, gelatinase and TNF convertase (TACE), and their modes of action, and also inhibitors thereof and their clinical effects, are described in WO-A-9611209, WO-A-9712902 and WO-A-9719075, the contents of which are incorporated
10 herein by reference. MMP inhibitors may also be useful in the inhibition of other mammalian metalloproteinases such as the adamalysin family (or ADAMs) whose members include TNF convertase (TACE) and ADAM-10, which can cause the release of TNF α from cells, and others, which have been demonstrated to be expressed by human articular cartilage cells and also involved in the destruction of myelin basic protein, a
15 phenomenon associated with multiple sclerosis.

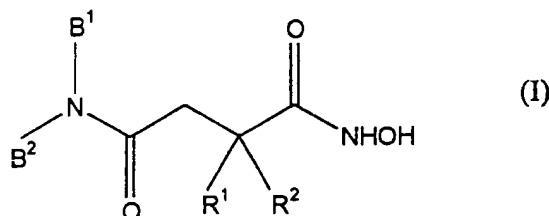
Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown, such as collagenase, stromelysin and gelatinase, have been shown to inhibit the release of TNF both *in vitro* and *in vivo*. See Gearing *et al* (1994), Nature 370:555-557; McGeehan *et al* (1994), Nature 370:558-561; GB-A-
20 2268934; and WO-A-9320047. All of these reported inhibitors contain a hydroxamic acid zinc-binding group, as do the imidazole-substituted compounds disclosed in WO-A-9523790. Other compounds that inhibit MMP and/or TNF are described in WO-A-9513289, WO-A-9611209, WO-A-96035687, WO-A-96035711, WO-A-96035712 and WO-A-96035714.

25 Further, somewhat related compounds are disclosed in US-A-5892112, WO-A-9724117 and FR-A-2597865.

Summary of the Invention

Compounds according to the invention are of formula (I):

5



10 wherein

R^1 is a group (optionally substituted with R^3) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl; and

R^2 is H or C_{1-6} alkyl;

15 or CR^1R^2 is cycloalkyl or heterocycloalkyl optionally substituted with R^3 or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl and C_{1-6} alkyl-heteroaryl;

R^3 is OR^7 , COR^7 , CO_2R^6 , $CON(R^7)_2$, $N(R^7)_2$, NR^7COR^7 , $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, $SO_2N(R^7)_2$ or cycloimidyl (optionally substituted with R^4);

20 R^4 is C_{1-6} alkyl;

B^1 and B^2 are the same or different and are each H or a group (optionally substituted with R^5) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, cycloalkenyl and heterocycloalkenyl; provided that B^1 and B^2 are

25 not both H, and that B^1-N-B^2 is not an α amino acid, ester or amide;

R^5 is R^6 or a group (optionally substituted with R^6) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl;

30 R^6 is a group selected from $N(R^7)_2$, NR^7COR^7 , $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, OR^7 , COR^7 , CO_2R^4 , $CON(R^7)_2$, $S(O)_{0-2}R^8$ and $SO_2N(R^7)_2$;

R^7 is H or a group selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-

heterocycloalkyl, wherein said group is optionally substituted with R^8 , COR^8 , $S(O)_{0-2}R^8$, CO_2R^8 , OR^8 , $CONR^4R^8$, NR^6R^8 or $SO_2NR^4R^8$ and for each case of $N(R^7)_2$ the R^7 groups are the same or different or $N(R^7)_2$ is heterocycloalkyl optionally substituted with R^8 , COR^8 , $S(O)_{0-2}R^8$, CO_2R^8 , OR^8 , $CONR^4R^8$, NR^6R^8 or $SO_2NR^4R^8$; and

- 5 R^8 is C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl or C_{1-6} alkyl-heteroaryl;
and the salts, solvates, hydrates, N-oxides, protected amino, protected carboxy and protected hydroxamic acid derivatives thereof.

Description of the Invention

- It will be appreciated that the compounds according to the invention can contain
10 one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres in a compound of formula (I) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

- It will further be appreciated that the compounds according to the invention may
15 contain an oxime. This oxime can give rise to geometrical isomers, and in each case the invention is to be understood to extend to all such isomers and mixtures thereof.

As used in this specification, alone or in combination, the term " C_{1-6} alkyl" refers to straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like.

- 20 The term " C_{2-6} alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2- methyl-2-propenyl etc.

- The term " C_{2-6} alkynyl" refers to a straight or branched chain alkyl moiety having
25 two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2- butynyl, 1- methyl-2-butynyl etc.

- The term "cycloalkyl" refers to a saturated alicyclic moiety having from three to six carbon atoms, which may be optionally benzofused at any available position. This includes for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, indanyl and the
30 like.

The term "cycloalkenyl" refers to an alicyclic moiety having from three to six carbon atoms and having in addition one double bond. This term includes, for example, cyclopentenyl and cyclohexenyl.

The term "heterocycloalkyl" refers to a saturated heterocyclic moiety having from
5 two to six carbon atoms and one or more heteroatom from the group N, O, S (or oxidised versions thereof) which may be optionally benzofused at any available position. This includes for example azetidiny, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, benzodioxole, tetrahydropyranyl, morpholinyl and the like.

The term "heterocycloalkenyl" refers to an alicyclic moiety having from three to
10 six carbon atoms and one or more heteroatoms from the group N, O, S and having in addition one double bond. This term includes, for example, dihydropyranyl.

The term "aryl" refers to an aromatic carbocyclic radical having a single ring or two condensed rings, optionally substituted with an aryl group substituent. This term includes, for example phenyl or naphthyl.

15 The term "heteroaryl" refers to aromatic ring systems of five to ten atoms of which at least one atom is selected from O, N and S, and optionally substituted with an aryl group substituent. This term includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.

The term "aryl group substituent" refers to a substituent chosen from halogen, CN,
20 CF_3 , CHF_2 , CH_2F , OCF_3 , OCF_2H , OCFH_2 and NO_2 .

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "benzofused" refers to the addition of a benzene ring sharing a common bond with the defined ring system.

The term "cycloimidyl" refers to a saturated ring of five to ten atoms containing
25 the atom sequence $-\text{C}(=\text{O})\text{NC}(=\text{O})-$. The ring may be optionally benzofused at any available position. Examples include succinimidoyl, phthalimidoyl and hydantoinyl.

The term "optionally substituted" means optionally substituted with one or more of the groups specified, at any available position or positions.

The terms "protected amino", "protected carboxy" and "protected hydroxamic
30 acid" mean amino, carboxy and hydroxamic acid groups which can be protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, *tert*-butoxycarbonyl, acetyl or like group, or may be in the form

of a phthalimido or like group. A carboxyl group can be protected in the form of a readily-cleavable ester such as the methyl, ethyl, benzyl or *tert*-butyl ester. A hydroxamic acid may be protected as either N or O-substituted derivatives, such as O-benzyl or O-*tert*-butyldimethylsilyl.

5 Salts of compounds of formula (I) include pharmaceutically-acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

10 Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

When the "protected carboxy" group in compounds of the invention is an esterified
15 carboxyl group, it may be a metabolically-labile ester of formula CO_2R^9 where R^9 may be an ethyl, benzyl, phenethyl, phenylpropyl, α or β -naphthyl, 2,4-dimethylphenyl, 4-*tert*-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzyloxymethyl or pivaloylmethyl group.

Preferably, R^1 is an optionally substituted C_{1-6} alkyl group, particularly a C_{1-6} alkyl
20 group. In compounds of this type, R^1 is most preferably an isopropyl group.

R^2 is preferably H.

An alternative preference is that, in compounds of the invention, CR^1R^2 is optionally substituted cycloalkyl or heterocycloalkyl, in particular, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidiny, pyrrolidinyl, piperidinyl, tetrahydrofuranyl
25 or tetrahydropyranyl. In compounds of this type, CR^1R^2 is preferably cyclobutyl, cyclopentyl, cyclohexyl or tetrahydropyranyl. Another preference is that CR^1R^2 is heterocycloalkyl.

B^1 is preferably H or optionally substituted C_{1-6} alkyl. More preferably, B^1 is a hydrogen atom or a C_{1-6} alkyl group, especially a methyl group.

30 In one embodiment of the invention, B^2 is a group, optionally substituted with R^5 , selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl.

A preferred group of compounds of this type is where B^2 is a group, optionally substituted with R^5 , selected from aryl, heteroaryl, cycloalkyl and heterocycloalkyl, particularly, optionally substituted aryl, cycloalkyl or heterocycloalkyl. In compounds of this type, B^2 is especially optionally substituted phenyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidiny, pyrrolidiny or piperidiny, particularly optionally substituted phenyl, cyclohexyl or piperidiny. Particular R^5 substituents are optionally substituted aryl, heteroaryl, cycloalkyl or heterocycloalkyl, especially optionally substituted aryl or heterocycloalkyl groups, such as phenyl, azetidiny, pyrrolidiny, tetrahydrofurany, piperidiny or morpholiny. In one particular embodiment, the heterocycloalkyl group is azetidiny, pyrrolidiny, tetrahydrofurany or piperidiny. In another, R^5 is morpholiny or phenyl optionally substituted by one or more aryl group substituents, in particular, F, Cl, CN, CF_3 , OCF_3 , OCF_2H or $OCFH_2$.

Another particular group of compounds of the invention is where B^2 is an optionally substituted C_{1-6} alkyl group, in particular, methyl, ethyl, propyl, butyl, pentyl or hexyl, especially ethyl or propyl. Particular R^5 substituents are optionally substituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, especially optionally substituted aryl, or R^6 , especially when R^6 is OR^7 . Preferred R^7 groups are aryl, heteroaryl, cycloalkyl or heterocycloalkyl, especially aryl. In compounds of this type the aryl group is in particular a phenyl group which is optionally substituted by one or more aryl group substituents, in particular, F, Cl, CN, CF_3 , OCF_3 , OCF_2H or $OCFH_2$.

R^6 (when present) may in particular be $N(R^7)_2$, NR^7COR^7 , $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, COR^7 , $S(O)_{0-2}R^8$, or $SO_2N(R^7)_2$. Especially preferred is where R^6 is $N(R^7)_2$, NR^7COR^7 , $NR^7CON(R^7)_2$, $S(O)_{0-2}R^8$, or $SO_2N(R^7)_2$, where for each case of $N(R^7)_2$ the R^7 groups are the same or different. Particular R^7 groups include a hydrogen atom, C_{1-6} alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl, in particular a hydrogen atom, a methyl group or a phenyl group optionally substituted by one or more aryl group substituents, in particular, F, Cl, CN, CF_3 , OCF_3 , OCF_2H or $OCFH_2$. R^8 is in particular C_{1-6} alkyl, aryl or heteroaryl, especially a methyl group or a phenyl group optionally substituted by one or more aryl group substituents, in particular, F, Cl, CN, CF_3 , OCF_3 , OCF_2H or $OCFH_2$.

A particularly useful group of compounds of the invention is that where R^1 is C_{1-6} alkyl, especially isopropyl, and R^2 is H; or CR^1R^2 is cycloalkyl or heterocycloalkyl,

especially cyclobutyl, cyclopentyl, cyclohexyl or tetrahydropyranyl; B¹ is H or C₁₋₆ alkyl, especially a hydrogen atom or a methyl group; and B² is an optionally substituted aryl, cycloalkyl or heterocycloalkyl group, particularly, optionally substituted phenyl, cyclohexyl or piperidinyl. Particular R⁵ substituents are optionally substituted aryl or heterocycloalkyl groups, especially, morpholinyl or phenyl optionally substituted by one or more aryl group substituents, in particular, F, Cl, CN, CF₃, OCF₃, OCF₂H or OCFH₂.

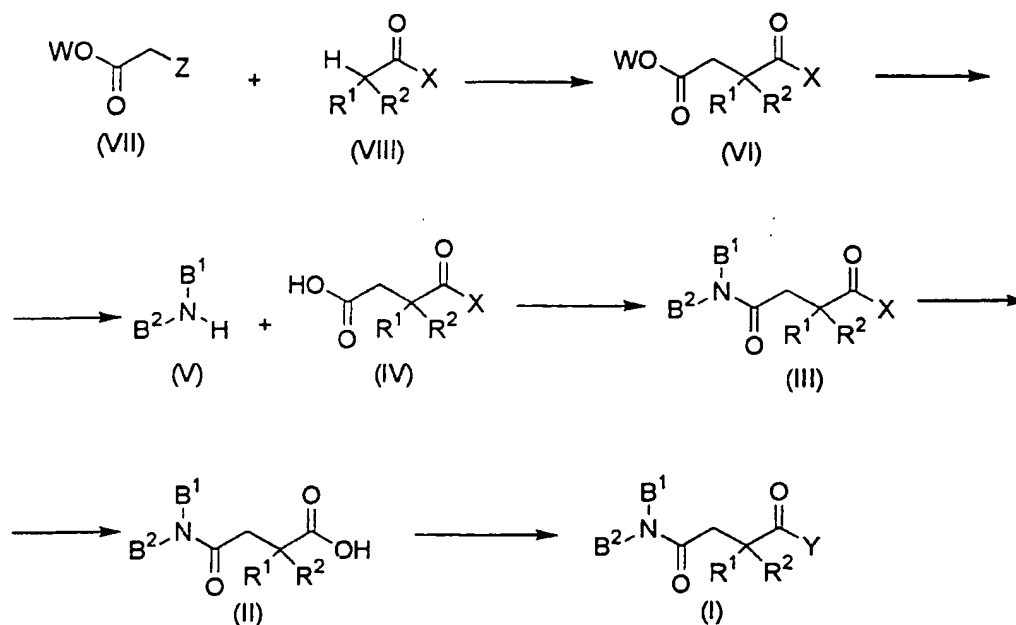
A further useful group of compounds of formula (I) is where R¹ is C₁₋₆ alkyl, especially isopropyl, and R² is H; or CR¹R² is cycloalkyl or heterocycloalkyl especially cyclobutyl, cyclopentyl, cyclohexyl or tetrahydropyranyl; B¹ is H or C₁₋₆ alkyl, especially a hydrogen atom or a methyl group; and B² is an optionally substituted C₁₋₆ alkyl group, especially ethyl or propyl. Particular R⁵ substituents are optionally substituted aryl, or R⁶ where R⁶ is OR⁷, in particular R⁷ is aryl. In compounds of this type, the aryl group is preferably a phenyl group which is optionally substituted by one or more aryl group substituents, in particular, F, Cl, CN, CF₃, OCF₃, OCF₂H or OCFH₂. Particularly preferred compounds from this group are where R¹ is isopropyl.

The compound of the Examples, and the salts, solvates, hydrates, N-oxides, protected amino, protected carboxy and protected hydroxamic acid derivatives thereof, are particularly preferred.

Compounds of the general formula (I) may be prepared by any suitable method known in the art and/or by the following processes. It will be appreciated that, where a particular stereoisomer of formula (I) is required, the synthetic processes described herein may be used with the appropriate homochiral starting material, and/or isomers can be resolved from mixtures using conventional separation techniques (e.g. HPLC). The compounds according to the invention may be prepared by the following process. In the description and formulae below, the groups R¹, R², B¹ and B² are as defined above, and Y is NHOH, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction sequence. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details, see Greene T.W. *et al*, "Protective Groups in Organic Synthesis", Wiley Interscience (1999).

Thus, for example, compounds of the invention may be prepared by the following general route:

5



Acids of formula (IV), where X is for example an alkoxy group, e.g. methoxy or ethoxy or a chiral auxiliary, e.g. *R*-4-benzyl-oxazolidin-2-one, may be prepared by deprotection of an ester of formula (VI) (where W is for example a *tert*-butyl or benzyl group) using, for example, an acid such as trifluoroacetic acid or by reaction with hydrogen in the presence of an appropriate catalyst such as palladium on carbon. Esters of formula (VI) may be prepared by reaction of an ester of formula (VII), wherein Z is an appropriate leaving group such as a halide, for example a bromide, or an alkyl or aryl sulfonate such as methanesulfonate, with an ester of formula (VIII). Suitable conditions for this reaction include the treatment of compound (VIII) with a strong organic base, such as lithium diisopropylamide or sodium hexamethyldisilazide, in an inert solvent such as tetrahydrofuran at an appropriate temperature such as -35°C to 0°C , followed by the slow addition of (VII).

Many esters of formulae (VII) and (VIII) or amines of formula (V) are known in the literature or may be prepared by standard methods known to those skilled in the art or by methods described in the examples herein after.

The acids of formula (IV) may be used to prepare compounds of formula (III) by
5 reaction with an amine of formula B_1B_2NH (V) using standard methods known to those skilled in the art, for example, by *in situ* activation of an acid of formula (IV) using for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, advantageously in the presence of catalyst such as 4-dimethylaminopyridine, in a halogenated hydrocarbon, e.g. dichloromethane, followed by subsequent addition of an
10 amine of formula (V). Alternatively, an acid of formula (IV) may be activated, for example by conversion to an acid halide such as an acid chloride by reaction with a halogenating agent such as oxalyl chloride, in the presence of a catalyst such as *N,N*-dimethylformamide in a halogenated hydrocarbon, e.g. dichloromethane. The acid chloride (which may or may not be isolated) can then be reacted with an amine of formula
15 (V) in the presence of an amine base such as triethylamine in a halogenated hydrocarbon, e.g. dichloromethane.

Carboxylic acids of formula (II) may be prepared by deprotection of a suitably protected carboxylic acid of formula (III), where X is removed for example by lithium hydroxide in the case of an alkyl ester, e.g. ethyl or lithium hydroxide/hydrogen peroxide
20 in the case of a chiral auxiliary such as *R*-4-benzyl-oxazolidin-2-one, using appropriate solvent and temperature conditions such as those described in the examples hereinafter.

The acids of formula (II) may be used to prepare compounds of formula (I) under conditions well known in the literature. For example, treatment of acids of formula (II) with oxalyl chloride in an inert solvent (such as dichloromethane) gives an intermediate
25 acid chloride, which may or may not be isolated, but which in turn is reacted with hydroxylamine at a suitable temperature such as room temperature to give the desired hydroxamic acids (I). Alternatively, an acid of formula (II) may be activated *in situ* using for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, advantageously in the presence of a catalyst such as a *N*-hydroxy
30 compound, e.g. *N*-hydroxybenzotriazole, using suitable conditions, e.g. in *N,N*-dimethylformamide at $-15^{\circ}C$, prior to the subsequent addition of a suitably protected hydroxylamine such as *tert*-butyldimethyl silyl hydroxylamine and warming to ambient

temperature. The protecting group maybe removed using appropriate conditions, such as water or tetrabutylammonium fluoride and acetic acid in tetrahydrofuran at 0°C, to yield the desired hydroxamic acids of formula (I).

Compounds of formula (I) may also be prepared by interconversion of other
5 compounds of formula (I). Thus, for example, a compound of formula (I) wherein R¹ is a C₁₋₆ alkyl group may be prepared by hydrogenation (using palladium on carbon in suitable solvent, such as an alcohol, e.g. ethanol) of a compound of formula (I) wherein R¹ is a C₂₋₆ alkenyl group.

Any mixtures of final products or intermediates obtained can be separated on the
10 basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

The compounds according to the invention exhibit *in vitro* inhibiting activities with
15 respect to the stromelysin, collagenase, gelatinase, ADAM or ADAM-TS enzymes. Compounds according to the invention may also exhibit *in vitro* inhibition of membrane shedding events known to be mediated by metalloproteinases, for example, α -APP, ACE, TGF- α , TNF- α , Fas ligand, selectins, TNFR-I, TNFR-II, CD30, IL-6R, CD43, CD44, CD16-I, CD16-II, Folate receptor, CD23, or IL-1RII.

20 The activity and selectivity of the compounds may be determined by use of the appropriate enzyme inhibition test, for example as described in Examples A-M of WO-A-9805635, by the assay for the inhibition of CD23 shedding described in WO-A-9924399 or by the assay of TNF RI shedding described in WO-A-0056704.

This invention also relates to a method of treatment for patients (including man
25 and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to metalloproteinases.

Accordingly, the compounds of formula (I) can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, and in diseases and indications resulting from the over-expression of these matrix metalloproteinases such as found in
30 certain metastatic tumour cell lines.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of TNF and MMPs. Accordingly in another aspect, this invention concerns:

5 a method of management (by which is meant treatment or prophylaxis) of disease or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and

a compound of formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions
10 mediated by TNF and/or MMPs; and

the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

The disease or conditions referred to above include inflammatory diseases,
15 autoimmune diseases, cancer, cardiovascular diseases, diseases involving tissue breakdown. Appropriate diseases include such as rheumatoid arthritis, osteoarthritis, osteoporosis, neurodegeneration, Alzheimer's disease, stroke, vasculitis, Crohn's disease, ulcerative colitis, multiple sclerosis, periodontitis, gingivitis and those involving tissue breakdown such as bone resorption, haemorrhage, coagulation, acute phase response,
20 cachexia and anorexia, acute infections, HIV infections, fever, shock states, graft versus host reactions, dermatological conditions, surgical wound healing, psoriasis, atopic dermatitis, epidermolysis bullosa, tumour growth, angiogenesis and invasion by secondary metastases, ophthalmological disease, retinopathy, corneal ulceration, reperfusion injury, migraine, meningitis, asthma, rhinitis, allergic conjunctivitis, eczema, anaphylaxis,
25 restenosis, congestive heart failure, endometriosis, atherosclerosis, endosclerosis, aspirin-independent anti-thrombosis, systemic lupus erythematosus and solid organ transplant.

Compounds of formula (I) may also be useful in the treatment of pelvic inflammatory disease (PID), age-related macular degeneration and cancer-induced bone resorption. Further, they can be used in the treatment of lung diseases, e.g. selected from
30 cystic fibrosis, adult respiratory distress syndrome (ARDS), emphysema, bronchitis obliterans-organising pneumonia (BOOP), idiopathic pulmonary fibrosis (PIF), diffuse

alveolar damage, pulmonary Langerhan's cell granulomatosis, pulmonary lymphangiomyomatosis (LAM) and chronic obstructive pulmonary disease (COPD).

For the treatment of all diseases and disorders previously indicated, the compounds of formula (I) may be administered orally, topically, parenterally, by inhalation spray or
5 rectally in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the treatment of
10 humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method
15 known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are
20 suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they
25 may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the US Patents 4,256,108; 4,166,452; and 4,265,874, to form osmotic therapeutic tablets for control
30 release.

Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate,

calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth,

naturally-occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and
5 flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension
10 may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's
15 solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of
20 suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc containing
25 the compounds of Formula (I) are employed. For the purposes of this specification, topical application includes mouth washes and gargles.

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 2.5 mg to about 7 g per patient per day). For example, inflammation may be
30 effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 g per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95% of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples illustrate the invention.

Intermediate 1 **(R)-4-Benzyl-3-(3-methylbutyryl)oxazolidin-2-one**

n-Butyllithium (33.0 ml, 1.6 M) was added to a solution of *R*-4-benzyl-oxazolidin-2-one (9.0 g) in tetrahydrofuran (100 ml) at -78 °C and the solution was stirred for 30 min, then a solution of isovaleryl chloride (6.1 g) was added dropwise over 20 min. The resulting suspension was stirred for 2 h, then aqueous ammonium chloride (saturated, 50 ml) was added and the volatiles removed *in vacuo*. The product was collected by filtration, washed with water (15 ml) and dried *in vacuo* to give the title compound (13 g) as a colourless solid.

*R*_f 0.45 (2:1 ether/hexane)

Intermediate 2 **3S-(4R-Benzyl-2-oxo-oxazolidine-3-carbonyl)-4-methylpentanoic acid *tert*-butyl ester**

Sodium hexamethyldisilazide (1.0 M in tetrahydrofuran, 23.0 ml) was added to a solution of Intermediate 1 (6.0 g) in tetrahydrofuran (100 ml) at -78 °C and the solution was stirred for 30 min, before a solution of *tert*-butyl bromoacetate (3.7 ml) in tetrahydrofuran (15 ml) was added dropwise. The mixture was stirred for 30 min, then allowed to warm to room temperature and ammonium chloride solution (saturated, 5 ml) added. The volatiles were removed *in vacuo* and the aqueous residue extracted with dichloromethane (3 x 10 ml). The solvent was washed with water (15 ml), brine

(15 ml), dried over magnesium sulphate (5 g) and the solvent removed *in vacuo* to give the title compound (8.6 g) as a colourless solid.

R_f 0.65 (3:2 hexane/ether)

Intermediate 3 3S-(4R-Benzyl-2-oxo-oxazolidine-3-carbonyl)-4-methyl
pentanoic acid

Trifluoroacetic acid (10 ml) was added to a solution of Intermediate 2 (8.6 g) in dichloromethane (50 ml) and the solution was stirred at room temperature for 2 h, before the volatiles were removed *in vacuo* and the residue azeotroped with heptane to dryness. The residue was dissolved in aqueous sodium bicarbonate (saturated, 10 ml) and washed with ether (2 x 10 ml), the aqueous layer acidified with citric acid and extracted with dichloromethane (3 x 10 ml). The dichloromethane extracts were washed with water (10 ml) and brine (10 ml), dried over magnesium sulphate (5 g) and the solvent removed *in vacuo* to give the title compound as a colourless oil (7.2 g) which crystallised slowly on standing.

15 R_f 0.45 (ether + 1% AcOH)

Intermediate 4 4-(4-Nitrophenyl)morpholine

4-Fluoronitrobenzene (5 g) and morpholine (7.2 g) were dissolved in ethanol (50 ml) and refluxed for 2 hr, before the ethanol was removed *in vacuo*. The resulting slurry was dissolved in ethyl acetate (30 ml) and washed with water (20 ml), dried over magnesium sulphate (2 g), and the solvent removed *in vacuo* to yield the title compound as an orange solid (7.3 g).

R_f 0.7 (ether)

Intermediate 5 **4-(Morpholin-4-yl)phenylamine**

To a stirred solution of Intermediate 4 (3.2 g) in ethanol (60 ml) were added hydrazine hydrate (3.71 ml) and palladium on charcoal (5%, 0.1 g). The reaction was stirred for 12 h, before being diluted with ethyl acetate (60 ml). The reaction was extracted with aqueous citric acid (5%, 4 x 15 ml), and the combined aqueous extracts neutralised with sodium bicarbonate. The aqueous was extracted with ethyl acetate (3 x 15 ml), and the combined organic extracts washed with brine (50 ml), dried over magnesium sulphate (2 g) and the solvent removed *in vacuo* to yield the title compound as a light brown oil (1.16 g).

R_f 0.31 (ether)

Intermediate 6 (4-(Morpholin-4-yl)phenyl)carbamic acid methyl ester

To a stirred solution of Intermediate 5 (0.3 g) in dichloromethane (30 ml) was added triethylamine (0.3 ml) and methyl chloroformate (0.15 ml). After 3 h, the dichloromethane was removed *in vacuo*, and the resulting slurry dissolved in ethyl acetate (20 ml), washed with aqueous citric acid (10 %, 15 ml), saturated aqueous sodium bicarbonate (15 ml) and brine (15 ml). The organic solvent was dried over magnesium sulphate (2 g), and the solvent removed *in vacuo* to yield the title compound as a yellow oil (0.26 g).

10 R_f 0.61 (ether)

Intermediate 7 Methyl-(4-(morpholin-4-yl)phenyl)amine

To a stirred solution of Intermediate 6 (0.26 g) in tetrahydrofuran (30 ml) was added lithium aluminium hydride (0.2 g). The reaction was stirred at room temperature for 12 h, before water (0.2 ml), aqueous sodium hydroxide (15 %, 0.2 ml) and water (0.6 ml) were added. The precipitates were removed by filtration and the filtrate dried over magnesium sulphate (2 g) and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography (silica, eluent 1 % methanol/dichloromethane) to yield the title compound as a brown solid (0.07 g).

MS 193 (M+1)

20 **Intermediate 8** 3S-(4R-Benzyl-2-oxo-oxazolidine-3-carbonyl)-4-methyl-pentanoic acid methyl-(4-morpholin-4-ylphenyl)amide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.20 g) was added to a solution of Intermediate 3 (0.32 g) in dichloromethane (20 ml) and the solution was stirred for 30 min, then a solution of Intermediate 7 (0.25 g) was added and the mixture was stirred overnight. The solvent was removed *in vacuo* and the resulting slurry dissolved in ethyl acetate (20 ml), washed with water (10 ml), aqueous sodium bicarbonate (saturated, 10 ml) and brine (10 ml), dried over magnesium sulphate (1 g) and evaporated to give the title compound (0.17 g) as a colourless oil.

R_f 0.64 (5 % methanol/dichloromethane)

Intermediate 9 3-Methyl-2-[[methyl-(4-(morpholin-4-yl)phenyl)carbamoyl]-methyl]butyric acid

Lithium hydroxide (0.02 g) in water (2 ml) was added to a solution of Intermediate 8 (0.17 g) in tetrahydrofuran (10 ml), water (5 ml) and aqueous hydrogen
5 peroxide (8M, 0.11 ml) at 0°C, and the mixture was stirred for 18 h. Sodium sulfite (0.21 g) in water (10 ml) was added and the mixture was evaporated *in vacuo*. The aqueous residue was washed with ether (2 x 10 ml), then acidified with citric acid and extracted with dichloromethane (2 x 20 ml), the combined dichloromethane extracts were washed with water (30 ml), brine (30 ml), dried over magnesium sulphate (1 g)
10 and evaporated to give the title compound (0.09 g) as a colourless oil.

R_f 0.55 (10% methanol/dichloromethane)

Intermediate 10 2-Isopropylsuccinic acid 1-ethyl ester

n-Butyllithium (1.6 M in hexane, 20.16 ml) was added to a stirred solution of diisopropylamine (4.52 ml) in tetrahydrofuran (60 ml) at -78 °C. After 15 min, ethyl
15 isovalerate (4.03 ml) was added and the reaction left for 1 h, before *tert*-butyl bromoacetate (4.78 ml) was added and the reaction allowed to warm to 0 °C. After 12 h water (10 ml) was added and the solvent removed *in vacuo*. The resulting slurry was extracted with ethyl acetate (3 x 20 ml), and the combined organic extracts washed with water (2 x 50 ml), brine (50 ml), dried over magnesium sulphate (2 g), and the solvent
20 removed *in vacuo* to yield a brown oil. The oil was dissolved in dichloromethane (60 ml) and trifluoroacetic acid (12 ml) was added and the reaction stirred for 12 h. The reaction was evaporated *in vacuo* and the residue azeotroped with heptane to dryness. The residue was dissolved in aqueous sodium hydroxide (2M, 40 ml) and washed with dichloromethane (2 x 10 ml), the aqueous layer acidified with hydrochloric acid (2M)
25 and extracted with ethyl acetate (3 x 10 ml). The combined ethyl acetate extracts were washed with water (10 ml) and brine (10 ml), dried over magnesium sulphate (2 g) and evaporated to give the title compound as a brown oil (4.5 g).

R_f 0.62 (30% hexane/ethyl acetate)

Prepared in a similar manner were:

Intermediate 11 1-Carboxymethylcyclobutanecarboxylic acid ethyl ester

From ethyl cyclobutanecarboxylate (2 g) and *tert*-butyl bromoacetate (2.76 ml), with purification by flash chromatography (eluent 20 % ethyl acetate/heptane), the title compound was obtained as a pale yellow oil (0.81 g).

5 R_f 0.27 (20% ethyl acetate/heptane)

Intermediate 12 4-Carboxymethyltetrahydropyran-4-carboxylic acid methyl ester

From tetrahydropyran-4-carboxylic acid methyl ester (2 g) and *tert*-butyl bromoacetate (2.33 ml), the title compound was obtained as a brown oil (3.95 g).

10 MS 201 (M-1)

Intermediate 13 4-Phenylcyclohexanone oxime

To a stirred solution of 4-phenylcyclohexanone (5 g) in ethanol (100 ml) and acetic acid (16.4 ml) was added aqueous hydroxylamine (50 %, 4.5 ml). The reaction was heated at reflux for 16 h, before being allowed to cool, and diluted with
15 dichloromethane (100 ml). The reaction was washed with aqueous sodium bicarbonate (sat, 2 x 50 ml), the organic layer dried over magnesium sulphate (2 g) and the solvent removed *in vacuo* to yield a white solid. This was purified by flash chromatography (silica, eluent 50 % ethyl acetate/hexane), to yield the title compound as a white solid (5.1 g).

20 R_f 0.36 (50 % ethyl acetate/hexane)

Intermediate 14 4-Phenylcyclohexylamine

To a stirred solution of Intermediate 13 (5.1 g) and nickel chloride (12.8 g) in methanol (40 ml) at -30 °C, was added sodium borohydride (10.2 g). The reaction was stirred at -30 °C for 30 min, before being stirred at room temperature for 16 h. The
25 solvent was removed *in vacuo*, and the black slurry was dissolved in aqueous hydrochloric acid (2M, 300 ml), and washed with ethyl acetate (3 x 200 ml). The aqueous layer was then basified to pH 10 using solid sodium hydroxide, and EDTA added until the solution stayed blue. The aqueous was then extracted with ethyl acetate (3 x 200 ml), the combined organic extracts dried over magnesium sulphate (4 g), and
30 the solvent removed *in vacuo* to yield the title compound as a white oily solid (3.2 g).

MS 190 M+1

Intermediate 15 3-Methyl-2-[(4-phenylcyclohexylcarbamoyl)methyl]butyric acid ethyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.80 g) was added to a solution of 4-dimethylaminopyridine (0.04g) and Intermediate 10 (0.54 g) in dichloromethane (30 ml) and the solution was stirred for 30 min, then a solution of Intermediate 14 (0.50 g) in dichloromethane (5 ml) was added and the mixture was stirred overnight. The solvent was removed *in vacuo* and the resulting slurry dissolved in ethyl acetate (100 ml), washed with water (10 ml), aqueous sodium bicarbonate (10 ml) and brine (10 ml), dried over magnesium sulphate (1 g) and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography (silica, eluent 30 % ethyl acetate/hexane) to yield the title compound as a yellow solid (0.26 g).

R_f 0.24 (30% ethyl acetate/hexane)

Prepared in a similar manner were:

Intermediate 16 1-[(4-Phenylcyclohexylcarbamoyl)methyl]cyclobutane-carboxylic acid ethyl ester

From Intermediate 11 (0.53 g) and 4-phenylcyclohexylamine (0.50 g), with purification by flash chromatography (silica, eluent 30 % ethyl acetate/heptane), the title compound was obtained as a waxy white solid (0.35 g).

R_f 0.20 (30% ethyl acetate/heptane)

Intermediate 17 4-[(4-Phenylcyclohexylcarbamoyl)methyl]tetrahydropyran-4-carboxylic acid methyl ester

From Intermediate 10 (0.5 g) and Intermediate 14 (0.58 g), with purification by flash chromatography (silica, eluent 5% methanol/dichloromethane) the title compound was obtained as a white solid (0.28 g).

R_f 0.20 (30% ethyl acetate/heptane)

MS 360 (M+1)

Intermediate 18 2-(Indan-2-ylcarbamoylmethyl)-3-methylbutyric acid ethyl ester

From Intermediate 10 (0.55 g) and 2-aminoindane (0.5 g), with purification by flash chromatography (silica, eluent 30 % ethyl acetate/heptane), to yield the title compound as a white fluffy solid (0.56 g).

R_f 0.30 (30% ethyl acetate/heptane)

Intermediate 19 **2-(4-Chlorophenoxy)-N-methylacetamide**

To a stirred solution of 4-chlorophenoxyacetyl chloride (2 g) in tetrahydrofuran (40 ml) at 0°C was added methylamine (2M, 12.2 ml). The reaction was allowed to warm to room temperature, and stirred for 1 h, before water (30 ml) added and the tetrahydrofuran removed *in vacuo*. The aqueous was extracted with ethyl acetate (2 x 50 ml), the combined organic extracts washed with brine (40 ml), dried over magnesium sulphate (1 g) and the solvent removed *in vacuo* to yield the title compound as a white solid (1.67 g).

10 R_f 0.26 (60 % ethyl acetate/hexane)

Intermediate 20 **[2-(4-Chlorophenoxy)ethyl]methylamine**

To a stirred solution of Intermediate 19 (0.84 g) in tetrahydrofuran (30 ml) at 0 °C was added lithium aluminium hydride (0.64 g). The reaction was stirred at room temperature for 3 h, followed by reflux for 2 h. On cooling water (0.64 ml), aqueous sodium hydroxide (15%, 0.64 ml) and water (1.9 ml) were added. The precipitates were removed by filtration and the filtrate diluted with ethyl acetate (30 ml) and extracted with aqueous hydrochloric acid (2M, 2 x 30 ml). The aqueous layer was basified to pH 12 with aqueous sodium hydroxide (2M), and extracted with methanol/dichloromethane (10 %, 2 x 50 ml). The combined organic extracts were washed with brine (40 ml) dried over magnesium sulphate (2 g) and the solvent removed *in vacuo* to yield the title compound as a pale yellow oil (0.32 g).

R_f 0.45 (20 % methanol/dichloromethane)

Intermediate 21 **3-(4-Chlorophenyl)propionaldehyde**

To a stirred solution of oxalyl chloride (2.04 ml) in dichloromethane (40 ml) at -78 °C was added dimethyl sulphoxide (3.33 ml), and the reaction stirred for 10 min. 3-(4-Chlorophenyl)propanol (2.0 g) in dichloromethane (20 ml) was added and the reaction stirred at -78 °C for 75 min. Triethylamine (11.53 ml) was added, the reaction allowed to warm to room temperature, and stirred for 30 min. Water (150 ml) was added, and the reaction extracted with dichloromethane (2 x 100 ml). The combined organic extracts were washed with water (3 x 100 ml), dried over magnesium sulphate (2 g), and the solvent removed *in vacuo* to yield a yellow oil. This was purified by

flash chromatography (silica, eluent dichloromethane) to yield the title compound as a pale yellow oil (0.96 g).

R_f 0.77 (dichloromethane)

Intermediate 22 [3-(4-Chlorophenyl)propyl]methylamine

5 Intermediate 21 (0.35 g), methylamine (2.07 ml, 2M solution in tetrahydrofuran) were stirred together in tetrahydrofuran (15 ml) for 5 min, before sodium triacetoxyborohydride (1.32 g) was added. The reaction was stirred for 18 h, before water (10 ml) was added, and the tetrahydrofuran was removed *in vacuo*. The resulting slurry was washed with ethyl acetate (3 x 50 ml), and then basified to pH 11
10 using sodium hydroxide (2M). The aqueous was then re-extracted with ethyl acetate (3 x 50 ml). These combined organic extracts were washed with brine (100 ml), dried over magnesium sulphate (1 g), and the solvent removed *in vacuo* to yield the title compound as a colourless oil (0.13 g).

R_f 0.13 (10 % methanol/dichloromethane)

15 **Intermediate 23 2-([2-(4-Chlorophenoxy)ethyl]methylcarbamoyl)methyl-3-methylbutyric acid ethyl ester**

 Intermediate 10 (0.32 g) was dissolved in dichloromethane (15 ml), and oxalyl chloride (0.3 ml) and *N,N*-dimethylformamide (1 drop) were added. The reaction was stirred for 1 h before the solvent was removed *in vacuo*. The resulting solid was
20 dissolved in dichloromethane (20 ml) and Intermediate 20 (0.32 g) was added, followed by triethylamine (0.48 ml). The reaction was stirred at room temperature for 16 h. The reaction was diluted with dichloromethane (10 ml), washed with water (40 ml), aqueous sodium hydroxide (2M, 40 ml), aqueous sodium bicarbonate (40 ml) and brine (40 ml), dried over magnesium sulphate (1 g) and evaporated to give the title compound (0.17
25 g) as a colourless oil.

R_f 0.5 (40% hexane/ethyl acetate)

The following was prepared in a similar manner.

Intermediate 24 2-([3-(4-Chlorophenyl)propyl]methylcarbamoyl)methyl-3-methylbutyric acid ethyl ester

30 From Intermediate 14 (0.15 g) and Intermediate 22 (0.13 g) to yield the title compound as orange oil (0.19 g).

R_f 0.64 (30% hexane/ethyl acetate)

Intermediate 25 2-([2-(4-Chlorophenoxy)ethyl]methylcarbamoyl)methyl)-3-methylbutyric acid

To a stirred solution of Intermediate 23 (0.49 g) in tetrahydrofuran (5 ml) and
5 methanol (5 ml) was added lithium hydroxide (0.29 g) in water (5 ml). The reaction
was heated to 40 °C for 16 h, before being allowed to cool, and the solvent removed
in vacuo. The residue was taken up in water (15 ml) and washed with ethyl acetate (2
x 10 ml), then acidified with citric acid and extracted with ethyl acetate (2 x 20 ml).
The combined ethyl acetate extracts were washed with brine (30 ml), dried over
10 magnesium sulphate (1 g) and evaporated to give the title compound (0.39 g) as a
yellow oil.

R_f 0.29 (40% hexane/ethyl acetate)

The following were prepared in a similar manner.

Intermediate 26 3-Methyl-2-[(4-phenylcyclohexylcarbamoyl)methyl]butyric
15 acid

From Intermediate 23 (0.26 g), to yield the title compound as a white foam
(0.21 g).

R_f 0.50 (10% methanol/dichloromethane)

Intermediate 27 1-[(4-Phenylcyclohexylcarbamoyl)methyl]cyclobutane
20 carboxylic acid

From Intermediate 16 (0.34 g) to yield the title compound as a white solid (0.24
g).

R_f 0.46 (10% methanol/dichloromethane)

Intermediate 28 4-[(4-Phenylcyclohexylcarbamoyl)methyl]tetrahydropyran-4-
25 carboxylic acid

From Intermediate 17 (0.28 g) to yield the title compound as a white solid (0.19
g).

R_f 0.41 (10% methanol/dichloromethane)

Intermediate 29 2-(Indan-2-ylcarbamoylmethyl)-3-methylbutyric acid

30 From Intermediate 18 (0.56 g), to yield the title compound as a white solid
(0.22 g).

R_f 0.3 (5 % methanol/dichloromethane)

Intermediate 30 2-({[3-(4-Chlorophenyl)propyl]methylcarbamoyl}methyl)-3-methylbutyric acid

From Intermediate 24 (0.19 g), heated at 60 °C to yield the title compound as
5 a yellow gum (0.14 g).

R_f 0.4 (30 % hexane/ethyl acetate)

Example 1 2(S)-N¹-Hydroxy-2-isopropyl-N⁴-methyl-N⁴-[4-(morpholin-4-yl)phenyl]succinamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.06 g) and N-
10 hydroxybenzotriazole (0.04 g) were added to a solution of Intermediate 9 (0.09 g) in
N,N-dimethylformamide (5 ml) at -15 °C and the mixture was stirred for 30 min, then
tert-butyldimethyl silyl hydroxylamine (0.07 g) was added and the reaction stirred for 2 h.
The mixture was allowed to warm to room temperature and stirred for 18 h. Water (10
ml) was added and the mixture extracted with ethyl acetate (2 x 15 ml). The solvent was
15 washed with water (15 ml), aqueous sodium bicarbonate (15 ml) and brine (15 ml), dried
over magnesium sulphate (1 g) and evaporated. The residue was purified by reverse phase
preparative HPLC using a 25cm x 21.4mm Phenomenex Luna C18 (2) (5u) column and
a mobile phase of aqueous formic acid (0.1% v/v) and acetonitrile under gradient
conditions from 5% to 55% acetonitrile. The title compound (0.007 g) was obtained as
20 a white solid, >99% pure by HPLC analysis.

R_f 0.34 (5% methanol/dichloromethane)

MS 380 (M+1)

Example 2 N⁴-[2-(4-Chlorophenoxy)ethyl]-N¹-hydroxy-2-isopropyl-N⁴-methylsuccinamide

25 A solution of Intermediate 25 (0.31 g) in dichloromethane (15 ml) was treated with
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.21 g) and O-*tert*-
butyldimethylsilylhydroxylamine (0.17 g) and the mixture was stirred for 18 h, then
washed with water (40 ml), and the aqueous extracted with dichloromethane (20 ml). The
combined organic extracts were dried over magnesium sulphate (1 g) and evaporated to
30 give a yellow gum. This was taken up in tetrahydrofuran (20 ml), cooled to 0 °C and
tetrabutylammonium fluoride (1M, 1.08 ml) added and the reaction stirred for 8 min,

before acetic acid (2 drops) was added. The solvent was removed *in vacuo*, water (10 ml) was added, and the slurry extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed with brine (30 ml), dried over magnesium sulphate (0.5 g) and the solvent removed *in vacuo*. Purification by flash chromatography (silica, eluent 5 % methanol/dichloromethane) yielded the title compound as a gummy solid (0.023g).

R_f 0.38 (5% methanol/ethyl acetate)

MS 343 (M+1)

The following Examples were prepared in a similar manner.

10 **Example 3** **N¹-Hydroxy-2-isopropyl-N⁴-(4-phenylcyclohexyl)succinamide**

From Intermediate 26 (0.21 g), to yield the title compound as a beige solid (0.11 g).

R_f 0.43 (10% methanol/dichloromethane)

MS 318 (M⁺)

15 **Example 4** **1-[(4-Phenylcyclohexylcarbamoyl)methyl]cyclobutane
carboxylic acid hydroxyamide**

From Intermediate 27 (0.24 g), with purification by reverse phase preparative HPLC using a 25 cm x 21.4 mm Phenomenex Luna C18 (2) (5u) column and a mobile phase of aqueous formic acid (0.1% v/v) and acetonitrile under gradient conditions from 5% to 75% acetonitrile. The title compound (0.07 g) was obtained as a white solid, >99% pure by HPLC analysis.

R_f 0.22 (10% methanol/dichloromethane)

MS 331 (M+1)

25 **Example 5** **4-[(4-Phenylcyclohexylcarbamoyl)methyl]tetrahydropyran-4-
carboxylic acid hydroxyamide**

From Intermediate 28 (0.19 g) with purification by reverse phase preparative HPLC using a 25 cm x 21.4 mm Phenomenex Luna C18 (2) (5u) column and a mobile phase of aqueous formic acid (0.1% v/v) and acetonitrile under gradient conditions from 5% to 75% acetonitrile. The title compound (0.05 g) was obtained as a white solid, >99% pure by HPLC analysis.

R_f 0.53 (10% methanol/dichloromethane)

MS 361 (M+1)

Example 6 **N¹-Hydroxy-N⁴-(indan-2-yl)-2-isopropylsuccinamide**

From Intermediate 29 (0.22 g), with purification by reverse phase preparative HPLC using a 25 cm x 21.4 mm Phenomenex Luna C18 (2) (5u) column and a mobile phase of aqueous formic acid (0.1% v/v) and acetonitrile under gradient conditions from 5% to 75% acetonitrile. The title compound (0.051 g) was obtained as a white solid, >98% pure by HPLC analysis.

R_f 0.26 (10% methanol/ethyl acetate)

MS 291 (M+1)

Example 7 **N⁴-[3-(4-Chlorophenyl)propyl]-N¹-hydroxy-2-isopropyl-N⁴-methylsuccinamide**

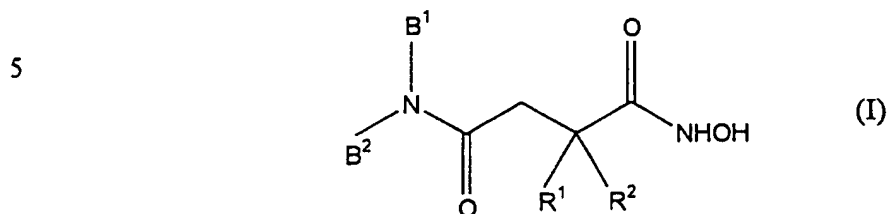
From Intermediate 30 (0.4 g), with purification by flash chromatography (silica, eluent 5 % methanol/ethyl acetate) to yield the title compound as a glassy solid (0.034 g).

R_f 0.4 (5% methanol/ethyl acetate)

MS 342 (M+1)

CLAIMS

1. A compound of formula (I)



10

wherein

R^1 is a group (optionally substituted with R^3) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl; and

15

R^2 is H or C_{1-6} alkyl;

or CR^1R^2 is cycloalkyl or heterocycloalkyl optionally substituted with R^3 or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl and C_{1-6} alkyl-heteroaryl;

20 R^3 is OR^7 , COR^7 , CO_2R^6 , $CON(R^7)_2$, $N(R^7)_2$, NR^7COR^7 , $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, $SO_2N(R^7)_2$ or cycloimidyl (optionally substituted with R^4);

R^4 is C_{1-6} alkyl;

B^1 and B^2 are the same or different and are each H or a group (optionally substituted with R^5) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, cycloalkenyl and heterocycloalkenyl; provided that B^1 and B^2 are not both H, and that B^1-N-B^2 is not an α amino acid, ester or amide;

25

R^5 is R^6 or a group (optionally substituted with R^6) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl;

30

R^6 is a group selected from $N(R^7)_2$, NR^7COR^7 , $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, OR^7 , COR^7 , CO_2R^4 , $CON(R^7)_2$, $S(O)_{0-2}R^8$ and $SO_2N(R^7)_2$;

R^7 is H or a group selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl, wherein said group is optionally substituted with R^8 , COR^8 , $S(O)_{0-2}R^8$, CO_2R^8 , OR^8 , $CONR^4R^8$, NR^6R^8 or $SO_2NR^4R^8$ and for each case of $N(R^7)_2$ the R^7 groups are the same or different or $N(R^7)_2$ is heterocycloalkyl optionally substituted with R^8 , COR^8 , $S(O)_{0-2}R^8$, CO_2R^8 , OR^8 , $CONR^4R^8$, NR^6R^8 or $SO_2NR^4R^8$; and

R^8 is C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl or C_{1-6} alkyl-heteroaryl;
 10 or a salt, solvate, hydrate, N-oxide, protected amino, protected carboxy or protected hydroxamic acid derivative thereof.

2. A compound of claim 1, wherein R^1 is C_{1-6} alkyl.

3. A compound of claim 1 or claim 2, wherein R^2 is H.

4. A compound of claim 1, wherein CR^1R^2 is optionally substituted cycloalkyl or
 15 heterocycloalkyl.

5. A compound of any preceding claim, which is in the form of a single enantiomer or diastereomer.

6. A compound of claim 1, which is selected from

2*S*- N^1 -hydroxy-2-isopropyl- N^4 -methyl- N^4 -[4-(morpholin-4-yl)phenyl]succinamide,
 20 N^4 -[2-(4-chlorophenoxy)ethyl]- N^1 -hydroxy-2-isopropyl- N^4 -methylsuccinamide,
 N^1 -hydroxy-2-isopropyl- N^4 -(4-phenylcyclohexyl)succinamide,
 1-[(4-phenylcyclohexylcarbamoyl)methyl]cyclobutane carboxylic acid
 hydroxyamide,

4-[(4-phenylcyclohexylcarbamoyl)methyl]tetrahydropyran-4-carboxylic acid
 25 hydroxyamide,

N^1 -hydroxy- N^4 -(indan-2-yl)-2-isopropylsuccinamide, and

N^4 -[3-(4-chlorophenyl)propyl]- N^1 -hydroxy-2-isopropyl- N^4 -methylsuccinamide.

7. A pharmaceutical composition for use in therapy, comprising a compound as defined in any preceding claim, and a pharmaceutically-acceptable diluent or carrier.

8. Use of a compound according to any of claims 1 to 6, for the manufacture of a medicament for the treatment of cancer, asthma, inflammation, an inflammatory condition, an autoimmune, infectious or ocular disease, or age-related macular degeneration.

INTERNATIONAL SEARCH REPORT

Intern: 91 Application No
PCT/GB 00/04861

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/32 C07D295/18 A61K31/445 A61K31/495 A61P11/00
A61P19/00 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 892 112 A (GROBELNY DAMIAN ET AL) 6 April 1999 (1999-04-06) cited in the application column 44, line 5; claims ---	1,8,9
A	WO 97 24117 A (RHONE-POULENC RORER PHARMA ;GRONEBERG ROBERT D (US); NEUENSCHWANDE) 10 July 1997 (1997-07-10) cited in the application claims 1,22,61-70 ---	1,8,9
A	FR 2 597 865 A (ROUSSEL UCLAF) 30 October 1987 (1987-10-30) cited in the application page 15 -page 17; claims; example 8 -----	1,8,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *G* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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